MISSED ABORTION*

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DISCUSSION *by C. Frederic Fluhmann, M. D., San Francisco; Frank W. Lynch, M. D., San Francisco; Norman H. Williams, M. D., Los Angeles.*

THE belief has become traditional that a vigorous reaction on the part of the uterus will promptly expel the product of conception whenever the fetus dies. As a rule, it happens so; and yet an interval of six weeks often passes before the abortion occurs. Should the delay be longer—several months, rarely a year or more—many vexing questions will arise; some theoretical, others quite practical in their implications. At times the interwoven medical and social features assume a legal aspect, and may provoke a lawsuit. The best known illustration of this contingency relates to a distinguished British gynecologist, a generation ago, who failed to consider all the possibilities in the case of a prominent London woman whose husband had been absent in India a year when she aborted a disintegrating ovum which presented an early stage of development. That the husband could not be responsible for the pregnancy was the opinion the gynecologist expressed; and in the courts he lost a suit brought against him for defamation of character. In fact, the prolonged retention of a dead embryo created this embarrassing domestic situation. Missed abortion was the correct diagnosis.

FREQUENCY

Missed abortion of impressive duration was once thought to be an extraordinary complication. Now, we know, it occurs much more often than intimated by the report of E. Fraenkel,[1] in 1903, who was able to collect only 105 cases, including his own. Current textbooks reflecting the personal experience of their authors agree that its incidence has been underestimated. Thus, Taussig,[2] in a comprehensive monograph just published, says that one-tenth of all the abortions in his own practice were retained a sufficient length of time to permit classification as "the missed" variety.

This complication is treated somewhat more frequently in private practice than in institutions which serve the poor. Malnutrition, fatigue, jolts and jars, hard work of all kinds, favor abortion whether the fetus is alive or dead. Among the well-to-do, on the other hand, when premonitory symptoms develop, treatment becomes insistent and often succeeds in abating a stimulus that otherwise would set in motion the expulsive muscular mechanism. The elimination of exercise, enforced rest to the point of keeping a patient in bed, and the abundant administration of sedatives, all assist toward defeating nature in her purpose to rid the woman of a fruitless pregnancy. And so, paradoxically, modern precautionary measures which safeguard the prospective mother increase the incidence of missed abortion.

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REPORT OF CASES

CASE 1.—Age, 23. Gravida 1. Last menstrual period began September 13, 1930. Normal progress for four months: never felt fetal movements. January 5, 1931, fundus nine centimeters above symphysis. January 14, abdominal pain of moderate intensity, one day; no bleeding. January 21, uterus the same size as one month ago. February 18, uterus smaller than at last visit and cannot be felt abdominally; on vaginal examination, found a retroverted uterus about the size characteristic at third month of pregnancy. General health excellent. When told of possibility of missed abortion, the patient insisted nothing was wrong.

Operation.—February 27. Dilatation of cervix and removal of ovum with placental forceps; curettement.

Pathologic Report.—Fragments of placenta. Fetus nine centimeters long; tissues dry and tough (mummification). Microscopic study shows shrunken chorionic villi. Endometrium regenerating: stroma cells small, glands resemble those of nonpregnant uterus rather than of decidua. Estimated retention period of dead fetus was three months.

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CASE 2.—Age, 43. Gravida 10. Eight living children; miscarriage at three months in 1922. L. M. P., January 5, 1927. Mild attack of influenza in February. X-ray treatments for pruritus vulvae during March and April. Slight vaginal bleeding for two days early in May and again on May 26; no cramps or backache. On June 11 she arrived in Los Angeles after a transcontinental railway journey, and shortly after reaching the hotel she noticed vaginal bleeding. The husband, a physician, thought pregnancy out of the question. The uterus, asymmetrically enlarged, corresponded in size with the third month of gestation. A round mass within the uterus at the right cornu, four centimeters in diameter, was interpreted as a myoma.

Operation.—June 14. Dilatation of cervix; digital exploration of uterine cavity. The mass just mentioned proved to be an hematoma mole. Contents of the uterus removed with placenta forceps; cavity packed with gauze. Bleeding scant until pack was removed after being in place twenty-four hours. Subsequently, excessive lochia for ten days, when uterine cavity was explored and no placental fragments found. At husband's request, radiation was employed and bleeding ceased. Recovery.

Pathologic Report.—Placenta penetrated by and covered with old blood-clots (Breus mole). In the center of the mass was a macerated embryo 3.5 centimeters long. Estimated retention period was four months.

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CASE 3.—Age, 35. Gravida 2. One living child delivered by low forceps on account of maternal toxemia (albuminuria). L. M. P., February 16, 1931. No ailments in early months. June 12, fundus eight centimeters above symphysis. July 13, no quickening; uterus the same size as a month ago; slight cramps and "spotting." On August 13 the hormonal urine test (Friedman) was negative.

Operation.—August 15. Dilatation of cervix and removal of uterine contents with placental forceps.

Pathologic Report.—Fetal sac intact, containing macerated embryo nine centimeters long. Estimated retention period was three months.

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CASE 4.—Age, 32. Gravida 3.—Two illegal abortions. L. M. P., May 15, 1930. When first seen, July 20, the uterus was enlarged and soft, but could not be outlined clearly on account of chronic inflammatory adnexal disease. The hormonal urine test (Friedman) was negative. July 31, severe abdominal cramps and moderate uterine bleeding.

Operation.—July 31. Dilatation of cervix; removal of uterine contents with placental forceps.

Pathologic Report.—Fetal sac intact, containing an amorphous lenticular mass, the embryo, one centimeter long, five millimeters thick. Estimated retention period was six weeks.

CASE 5.—Age, 23. Gravida 1. L. M. P., July 15, 1932. Her physician, consulted September 28, made a diagnosis of pregnancy. Quickening was never felt. No ailments. On February 3, 1933, as the abdomen failed to enlarge, the physician doubted the correctness of his primary diagnosis and was confused, especially by a negative hormonal urine test (Aschheim-Zondek). Then I saw the patient in consultation, and found the uterus approximately twice normal size: otherwise nothing noteworthy. Suspecting a missed abortion, dilatation and curettement were recommended. This was done by her physician, who reported the removal of placental tissue. Estimated retention period was six months.

CLASSIFICATION

How long must the dead fetus be retained before the diagnosis of missed abortion is warranted? Heretofore, attempts at definition, somewhat arbitrarily, were based upon a comparison of the developmental age of the embryo with the menstrual age of the pregnancy. Guided in that way, clinicians regarded a retention period of six weeks as requisite to correct classification. All the cases of this series fulfill that requirement: an interval of from six weeks to six months elapsed between the death of the fetus and the termination of pregnancy by instrumental means.

In the past no reasonable objection could be raised against the "time criterion"; but now, having at hand the hormonal urine test, it seems preferable to differentiate cases on that basis. In other words, the diagnosis of missed abortion, in my judgment, should be made only after the Aschheim-Zondek or Friedman reaction has become negative. Of course, it does not become so immediately after the fetus dies. As long as vitalized placental tissue remains, the test will be positive; until it becomes negative we must consider the possibility that the uterus will empty itself spontaneously. This suggestion, however, applies merely to the first half of pregnancy, the period corresponding with the accepted use of the term "abortion"; nearer term, Wilson and Corner [8] find that a positive hormonal urine reaction persists far too long after fetal death to serve the practical purposes of diagnosis and treatment.

The hormonal urine test was negative in three of my cases. Although not employed in the other two, they were correctly classified; the uterus of one of them contained a hematoma mole, the other a mummified fetus.

CLINICAL MANIFESTATIONS

In contrast with the frank, troublesome manifestations of most bodily derangements, the maternal symptoms of fetal death are conspicuous for their negative character. Breast engorgement vanishes, nausea and vomiting cease. A good appetite replaces a distaste for food. The tendency to lose weight is arrested; often the patient begins to gain, gradually and moderately. Relieved of the distinctive ailments of the early months, the prospective mother assumes everything is going as it should.

Invalidism in these cases, which impressed Litzenberg,[4] must be extraordinary. None of my patients complained of a foul taste, an offensive leukorrhea, chilly feelings, or malaise; neither were they profoundly anemic, feverish in the afternoon, or mentally disturbed. That infection seldom occurs is a remarkable fact, probably explained by organic readjustment to the changed embryologic situation. The muscular wall of the uterus becomes firmly retracted, its blood vessels undergo alterations which narrow the lumen and the endometrium begins to regenerate. None the less, precaution must be unremitting against the introduction of contaminating material; vaginal examinations, limited in number, will be made with strict aseptic technique and the marital relation forbidden.

A pregnant uterus of stationary or diminishing size provides the most significant clinical evidence of fetal death. At first the patient fails to notice that her abdomen is not growing larger; and, if she has not yet reached the time for quickening, this sign, or its absence, cannot be utilized. On clinical grounds the physician forms an opinion, beyond cavil, only after reëxamination of the patient at the end of a month. Meanwhile, if the laboratory reports a negative hormonal urine reaction, the debate is closed.

As a rule, very slight symptoms of threatened abortion follow directly upon fetal death, symptoms often insignificant to a patient accustomed to much more severe cramps with menstruation and indifferent to a faint discharge of blood. Should she communicate with her physician, he will recommend sedatives and continuous rest in bed. Typically these measures soon afford relief, and she resumes her customary routine for a longer or shorter interval until outspoken signs of abortion appear, or clear proof of fetal death warrants surgical treatment.

Neglected cases, women who first seek medical advice long after the fetus has perished, formerly presented great diagnostic difficulties. It was not easy to decide whether or not the uterus contained a pregnancy; and, if so, was the embryo alive? In these circumstances modern methods become most helpful, especially the hormonal urine test. A positive result impels delay; a negative one at least permits active treatment without the hazard of ending a pregnancy unwittingly. Even today, however, the differentiation of missed abortion and myoma can be perplexing, as I once had occasion to learn. Upon arrival from the East the patient began to bleed shortly after reaching a hotel and was brought to the hospital by her husband, a physician, who thought pregnancy out of the question. The history and the pelvic examination were in harmony with the diagnosis of myoma, but at operation a hematoma mole was found.

Clinical study seldom, if ever, discloses the cause for retention of the fetus. Consequently, in the case just mentioned it is noteworthy that repeated radiation had been used for the treatment of pruritus vulvae. In another case pelvic inflammatory disease had persisted since a former pregnancy was aborted illegally. There the chronic pathologic lesions, which included metritis, are suspected as responsible for uterine inertia. Isolated cases, to be sure, even correctly interpreted,

fail to indicate the broad principles which underlie prolonged retention of the fetus. For these we must look further.

PATHOLOGY

Anatomic research has taught a great deal with respect to the structural changes which precede and accompany the immature arrest of embryologic development. With a rich material, contributed by midwives as well as physicians, Mall [5] demonstrated in abortions that the primary defect of the gestational organization centers around the nutrition of the embryo, and that it dies before the placenta loses its vitality. Primarily, the maternal tissues are often at fault, but not always; the protoplasm of the embryo may be defective. Less intense grades of malnutrition, not severe enough to cause death, interfere with perfect embryonic development. These focal imperfections, in particular intra-uterine amputations, have been studied by Streeter.[6]

When the embryo dies, it becomes a foreign body—a permissible description for want of more exact information—and nature endeavors to cast it off. To this rule there are a few exceptions. A. W. Meyer [7] found that resorption of a conceptus occurs in women just as in multiparous mammals. He learned, too, that the embryo vanishes before the structures which protect it. This eventuality, of course, will be impossible unless development has ceased at an extremely early stage. Later the bulk and composition of the ovum prevent complete dissolution and absorption; it must then be removed by way of the birth canal. Presumably the uterus always tries to accomplish that result and occasionally fails because its contractions are either too infrequent or too weak.

Seeking the underlying cause of uterine inertia, it is not difficult to choose the path to follow. Let us see what help has already been had from endocrinal research. Of this there have been two pertinent varieties: one relates to the corpus luteum hormone, progesterone; the other to estrin, a hormone of great importance in fitting the uterus for parturition.

HORMONAL CONTROL

Snyder [8] demonstrated in the case of rabbits that the intravenous injection of urine from a pregnant woman postponed the birth of their young, and he attributed their retention in the uterus to the action of hormones. His conclusions were based upon a brilliantly conducted research the steps of which may be very briefly recapitulated. A small amount of chorionic gonadotrophic (anterior-pituitary-like) hormone thrown into the maternal circulation induced spurious ovulation, although the rabbits were already pregnant. The ovarian follicles which responded to this stimulus underwent the customary transformation into corpora lutea. Accordingly, parturition did not occur upon the ordinary date (thirty-two days postcoitus), but was deferred until the induced corpora completed their life cycle, postponing the delivery until the fortieth day, and prolonging pregnancy by a period 25 per cent of its usual duration. Specifically, the delay was due to the artificial production of corpora lutea and the consequent influence of their hormone. Snyder argues convincingly that the rabbit's uterine musculature remains quiescent during pregnancy in response to progesterone. Does the same reasoning apply to women? Probably so. At least this inference has the support of collateral evidence from other sources.

In 1903, L. Fraenkel [9] observed that women aborted when the corpus luteum was ablated in early pregnancy, or the ovary containing it removed. In other words, as it now appears, the depletion of progesterone permits the establishment of efficient uterine contractions. More recently, Corner and Allen [10] have shown that the corpus luteum functions in this way, among others. Clinical application of their work, reported by Falls, Lackner, and Krohn,[11] emphasizes the inhibitory effect of progesterone upon cases of habitual and threatened abortion.

It is significant, as Streeter remarks, that the expulsion of a conceptus is retarded conspicuously when fetal death occurs between the sixth and the seventeenth week of development. At this period the corpus luteum is relatively large; the placenta small; the amniotic fluid less abundant than later. Each of these environmental factors must be taken into account before the explanation for missed abortion becomes full and final: the corpus luteum because it produces progesterone, the fetal sac because its estrin content continues to be comparatively poor, while the bulk of the pregnancy remains small.

Estrin (also called female-sex hormone, theelin, progynon, folliculin, and by still other names) occurs not only in the fluid of the ovarian follicle, but also in the placenta, fetal membranes, and amniotic fluid. Unquestionably, it participates in the preparation of the uterus for the act of labor; but its sphere of influence has not been definitely ascertained. Some writers believe it sensitizes the muscle and nerve elements of this organ. Furthermore, Robinson and his coworkers [12] assume hypothetically that estrin stimulates the posterior lobe of the pituitary to elaborate the characteristic hormone, distinguished for its ecbolic properties.

If the pregnancy is normal the administration of estrin to women never causes abortion, according to Robinson, Datnow, and Jeffcoate; on the other hand these authors found the same treatment effective whenever a dead fetus was retained. Among twelve cases of missed abortion given massive doses of estrin, only two failed persistently to react, three responded following additional medication, the remaining seven expelled the contents of the uterus spontaneously, "after an interval up to seven or eight days." Parenthetically, estrin had no effect upon several patients with incomplete abortion and one with hydatid mole.

Such results will inspire further trial of this therapeutic agent, especially since Spielman, Goldberger, and Frank [13] reported several years ago that estrin disappears from the mother's blood after death of the fetus. During normal pregnancy its presence in the blood has long been recog-

nized, and its abundance in the urine was recently reaffirmed by Cohen, Marrian, and Watson,[14] who add: "the hormone first presents itself in an adynamic form, as estrone and estriol, in combination with glucuronic acid." At the approach of labor the bond is broken, liberating a potent form of estrin. Ultimately the functions of this endocrine secretion will be defined more clearly. At present it appears that during normal pregnancy two hormones, progesterone and estrin, hostile to each other in some respects, are equilibrated; preliminary to labor the latter gains the upper hand. Conversely, the inertia responsible for the prolonged retention of a dead fetus is probably associated with a deficiency of estrin and a surplus of progesterone.

TREATMENT

Radical treatment of missed abortion, either medical or surgical, must inevitably await proof of the death of the fetus. Subsequent delay will be governed largely by the patient's attitude, a permissible concession, for procrastination rarely leads to complications. Nevertheless, with the diagnosis established, the physician should recommend active treatment since the removal of the derelict pregnancy alone will restore the normal functions of the reproductive organs.

In due time the therapeutic merits of estrin will be fully ascertained. At present commercial preparations of the hormone are expensive and the correct dosage has not been announced. On theoretical grounds it was predicted that pituitrin would act weakly during the early months of pregnancy because of the antagonism of progesterone. So it does. Induction by means of bougies contributes infection too often and, besides, it frequently provokes bleeding. Therefore, when therapeutic abortion has been agreed upon, the logical choice of treatment today is surgical. If the attending physician in all conscience feels the need of assistance, there will be ample time to make such arrangements as best assure a satisfactory end-result.

In general the operation consists of dilating the cervix, loosening with a finger the retained material and removing it by the use of blunt forceps. A sharp instrument, a curette, may perforate the uterus. At times vaginal hysterotomy becomes the preferable operation. Irrespective of the type of procedure selected, preliminary preparations for packing the uterus are imperative to obviate postpartum hemorrhage.

As a rule the convalescence will be smooth, but in one case of this series, that of hematoma mole, excessive bleeding continued for days after removal of the pack. It ceased following radiation, employed at the request of the husband, a physician; sterility ensued. Likewise, the woman with chronic pelvic inflammatory disease has not become pregnant again. The remaining three patients have borne children subsequent to their experience of missed abortion. Finally, it should be noted that a few, very few, cases of repeated missed abortion have been recorded in medical literature.

SUMMARY

No longer a rare complication, missed abortion has had relatively slight comment in medical literature because until recently very little was known about the cause of the underlying uterine inertia when a dead fetus is retained. Negative clinical manifestations and relief from the common ailments of the early months of pregnancy mislead patients to believe that all is going well. Sound diagnosis will supplement the observation of arrested uterine growth with proof that the hormonal urine reaction has ceased to be positive. Anatomical studies reveal that the fetus dies before the placenta loses its vitality. Endocrinal research indicates a deficiency of estrin, a surplus of progesterone; a situation harmonious with persistent uterine inertia. In general treatment remains surgical, since drugs are almost always inert and hormonal therapy has not as yet been accurately defined. At operation two hazards must be kept in mind, perforation of the uterus and profuse hemorrhage.

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DISCUSSION

C. Frederic Fluhmann, M. D. (Stanford University Hospitals, San Francisco).—The condition of "missed abortion" is not only of considerable importance from a clinical standpoint, but it presents certain problems which are inevitably associated with the cause of the onset of

labor. As Doctor Slemons points out, modern investigators have sought to explain this phenomenon on an endocrinologic basis, and three main factors have been considered: (1) progestin, a specific product of the corpus luteum, which inhibits uterine motility; (2) estrin, which sensitizes the smooth muscle of the uterus so that it responds more readily to the oxytocic action of (3) the posterior pituitary principle. On the basis of animal experimentation, it has been possible to expound a number of theories; but it must be remembered that the problem in the human is complicated by the appearance of a new hormone which is not found in nonpregnant individuals nor under any conditions in ordinary laboratory animals. This substance, the "chorionic gonadotropic hormone," is present in large quantities in women during gestation, and its exact rôle in the physiology of pregnancy has not been determined. Although our attention is necessarily directed to an endocrinologic disorder as possibly responsible for the prolonged retention of a dead fetus and placenta in the uterus, one cannot escape the consideration of a disturbance in the uterus itself as a potential factor.

There is nothing to add to Doctor Slemons' discussion of the clinical manifestations, diagnosis, and treatment of missed abortion. On the Lane obstetric and gynecologic services, only eleven cases have been indexed under this diagnosis over a period of twenty years. I do feel, however, that the condition is more common than these figures and those quoted by most authors indicate, and we are very grateful to Doctor Slemons for bringing this subject to our attention.

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FRANK W. LYNCH, M.D. (University of California Medical School, San Francisco).—Doctor Slemons presents a thorough review of this rare condition and illustrates nearly all of its phases with cases from his own practice. His arguments are so convincing that there is very little that a discusser can say. As Doctor Slemons states, the complication in the past was shrouded with mysticism. Indeed, at one time it was believed that when the woman passed by the threatened abortion and did not extrude the contents of pregnancy, she in all likelihood would not abort until her expected date at term.

Before the discovery of the hormonal reactions of pregnancy, the diagnosis of the death of an early pregnancy was always a most difficult matter. Time in the final analysis gave the diagnosis; yet, when the patient was sick and when it did not seem reasonable to delay treatment more than absolutely necessary, confusion often reigned. It would not seem possible that there might be doubt as to whether the uterus had or had not increased in size from the third to the fourth month, yet very often there is such doubt. When Chadwick's sign had been present and disappeared, there was more than presumptive evidence that something was wrong. Yet Chadwick's sign very often does not appear until the last months of pregnancy. Even the blue discoloration along the middle of the anterior vaginal wall, extending to and about the anterior cervical lip, may be wanting. Yet, when you inspect the vagina of a woman with a missed abortion of six weeks to two months' standing, you will find it bears but little resemblance to the ordinary uterus of a four or five months' pregnancy.

The symptomatology is very interesting. Many women, but not all, develop malaise and symptoms that suggest protoplasmic poisoning. I have often wondered how many times I have been responsible for symptoms when I introduced doubt into the mind of some of my patients that the pregnancy was not developing. Certain it is that few of my patients were happy or contented while I was watching for definite proof that the case was a missed abortion. It is of interest, also, that the animal that has a missed abortion and absorbs the products of conception seldom, if ever, again becomes pregnant.

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NORMAN H. WILLIAMS, M.D. (1052 West Sixth Street, Los Angeles).—The subject of missed abortion is appropriate to a program of this kind; it is too seldom discussed. Medical literature relating to it is surprisingly scant. One who supervises obstetrical patients observes the occasional case, but Taussig's estimate of missed abortions as 10 per cent of all abortions seems high. Presumably the variable incidence, as stated by various observers, results from the present loose definition. Certainly, a definition dependent upon the time elapsing between the death of the fetus and its expulsion, or removal, from the uterus is uncertain; although this may be an aid to diagnosis. A definition based upon a negative biologic test for pregnancy seems more logical.

As Doctor Slemons suggests, the probable cause of the inertia lies in the unbalanced hormone production, the stimulus to uterine contractions thus being diminished. In all probability, cases will now be observed more carefully as experimental hormonal study becomes better standardized, and its clinical application made more certain.

In the event of missed abortion quite as much tact and judgment are required in handling the mental attitude of the patient and family, as in the treatment of the obstetrical complication. Carelessness there frequently leads to misunderstanding between the patient and her physician. One plausible reason for dissatisfaction lies in the fact that accurate diagnosis must necessarily be delayed; another relates to the infrequency of missed abortion. The laity is not familiar with such a possibility.

It is sound practice to empty the uterus as soon as the diagnosis is made. Procrastination may lead to embarrassment. In one instance, to my knowledge, missed abortion terminated on a ballroom floor.

THE LURE OF MEDICAL HISTORY†

A RARE BOOK*

REVIEW OF ONE OF THE VOLUMES IN THE GROWING COLLECTION IN THE LIBRARY OF THE LOS ANGELES COUNTY MEDICAL ASSOCIATION: FRIAR BARTHOLOMEW'S ENCYCLOPEDIA, BEST SELLER OF THE MIDDLE AGES

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"BARTHOLOMAEUS ANGLICUS' *De Proprietatibus Rerum,* 1491." So reads the prosaic index card, but far from prosaic is the story behind this card.

Some time between the years 1200 and 1240 A. D., Bartholomew the Englishman, monk of the Franciscan Order, set himself to the task of writing a comprehensive encyclopedia of contemporary lore. Thus was a medieval best-seller born. Busy pens—for this was before the day of the printing press—turned out copy after copy in Latin, Italian, French, Provencal, English, and Spanish. *De Proprietatibus Rerum* (On the Properties of Things)—for such was the name of this book—must have had great popular appeal, for only so can we explain its many translations into vernacular in a world where Latin was the language only of scholars. And only so can we explain the flood of editions which poured forth once 1440 had arrived and Gutenberg had invented printing and the necessary press.

The first printed edition, a Latin one, appeared at Basel about 1470, and by the beginning of the sixteenth century the presses had poured forth nine more Latin, five French, one Dutch, one English, and two Spanish editions. Thus from

†A Twenty-Five Years Ago column, made up of excerpts from the official journal of the California Medical Association of twenty-five years ago, is printed in each issue of CALIFORNIA AND WESTERN MEDICINE. The column is one of the regular features of the Miscellany department, and its page number will be found on the front cover.

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